1: Eur J Immunol 1982 Nov;12(11):967-72

Alloactivated long-term cultured human T lymphocytes express both HLA-DR and SB antigens but lack lymphocyte stimulation capacity.

Pawelec G, Blaurock M, Schneider EM, Shaw S, Wernet P.

Cell populations obtained from mixed leukocyte cultures of 6- or 10-day duration were found specifically to restimulate primed lymphocytes detecting HLA-linked SB as well as HLA-D-associated antigens. After expansion in vitro (9-75 days) with medium containing interleukin 2, the cultured cells expressed the T lymphocyte markers detected in indirect immunofluorescence by monoclonal antibodies Lyt-3, OKT3, OKT4, OKT8, and had high levels of HLA-DR antigens. In addition, they were shown in cell-mediated lymphocytotoxicity specifically to express SB antigens of the donor B cell type. Despite their positivity for DR and SB antigens, such cultured T cells failed to restimulate either SB- or D-specific secondary lymphocyte proliferation. Homogeneous cloned populations of cultured T cells also lacked lymphocyte stimulation capacity. In contrast, B cell lines, which also expressed DR and SB antigens, were potent stimulators of both SB- or D-directed proliferation. These data show that the activated T lymphocytes which express both HLA-DR and SB antigens are by themselves unable to stimulate lymphocyte proliferation.

PMID: 6983971 [PubMed - indexed for MEDLINE]

1: J Immunol 1983 May;130(5):2250-5

In vivo analysis of allogeneic lymphocyte interaction: activation of suppressor T cells by an I-J-restricted allogeneic effect factor (AEF).

Bromberg JS, Delovitch TL, Kaufman K, Greene MI.

The preceding paper detailed the production and fractionation of a T cell-derived I-J-specific allogeneic effect factor (AEF) and analyzed its ability to provide help in a T cell-depleted, in vitro primary anti-sheep erythrocyte response. The identical AEF fractions were examined in this study for their ability to elicit suppression in a delayed-type hypersensitivity assay. Previous reports showed that low or suboptimal doses of antigen, presented i.v. on a cell surface, induce a precursor or primed set of suppressor T cells (pre Ts). These cells manifested antigen-specific suppression only in the presence of a T cell-mediated I-J-specific allogeneic effect induced in vivo against the pre Ts. The experiments reported here examined the ability of alloactivated T cell-derived I-J-specific AEF components to replace the in vivo I-J allogeneic effect. The results show that certain AEF components can indeed provide the signal(s) necessary for activation of suppression. Size and charge separation of the crude AEF preparation revealed several components, some of which could independently serve as appropriate inductive signals. One of these components proved to be biochemically identical to interleukin 2 (IL 2) and accounted for some of the genetically unrestricted AEF activity observed; other higher m.w. molecules also possessed unrestricted activity. Another component provided the requisite activational signals and this 68,000-dalton, pI 5.6 molecule(s) was I-J restricted. These findings are discussed in terms of models of lymphocyte subset interactions and activation.

PMID: 6220087 [PubMed - indexed for MEDLINE]

☐ 1: Cancer 1985 Feb 1;55(3):552-60

Clinical response of a patient with diffuse histiocytic lymphoma to adoptive chemoimmunotherapy using cyclophosphamide and alloactivated haploidentical lymphocytes. A case report and phase I trial.

Kohler PC, Hank JA, Exten R, Minkoff DZ, Wilson DG, Sondel PM.

Adoptive chemoimmunotherapy has cured experimentally induced tumors in animals, but its clinical use has been limited. Six patients were treated with refractory neoplasms in a Phase I study with cyclophosphamide (CPM) and alloactivated haploidentical lymphocytes. Patients received an immunosuppressive dose of CPM (800 mg/m2) followed by haploidentical lymphocytes primed in vitro with alloantigens in mixed lymphocyte culture (MLC). One week later patients received a second infusion of alloactivated lymphocytes expanded in T-cell growth factor (TCGF). The total number of cells given to each patient progressively increased, with a single patient receiving 35.5 X 10(9) cells. Transient febrile responses and delayed-type hypersensitivity reactions at the intravenous sites were the only toxicities noted. A complete clinical response lasting 12 weeks was seen in a single patient with diffuse histiocytic lymphoma. Our experience indicates that adoptive chemoimmunotherapy can be given to patients safely and merits further clinical testing.

PMID: 3155491 [PubMed - indexed for MEDLINE]

Activation of macrophages by in vitro allostimulated T cells.

Whitten HD, Cruse JM, Fudenberg HH.

Murine peritoneal macrophages, parabiotically co-cultured with combinations of in vitro H-2 sensitized thymus-derived lymphocytes obtained from drug-pretreated mice, possessed an increased cytotoxicity against alloantibody-coated target cells. This heightened activity appeared to be accentuated by and dependent on T-cell synergy. After 5 days of in vitro allosensitization at 37 degrees C, cortisone-resistant thymocytes allosensitized in combination with cyclophosphamide-pretreated splenic T cells released molecules that produced strong antibody-dependent macrophage-mediated cytotoxicity (ADCC). This enhanced ADCC correlated with increased macrophage rosetting with IgG-sensitized erythrocytes. These heightened activities resulted from soluble mediators released by the activated T cells which diffused across a 0.22-microns Millipore filter and were not dependent on lymphocyte-macrophage contact. Evidence that these molecules originated from the highly enriched T-cell populations and were not synthesized de novo by macrophages was supported by results of pretreatment with protein and RNA synthesis inhibitors. Evidence that soluble Fc receptors released from the alloactivated T cells were responsible for the increased macrophage EA binding and ADCC was obtained in affinity chromatography experiments in which activity could be depleted by passage over a Sepharose-Fc-coupled column and recovered in the column eluate.

PMID: 6601296 [PubMed - indexed for MEDLINE]

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1: Br J Urol 1998 Oct;82(4):487-93

Autologous and allogenic hybrid cell vaccine in patients with metastatic renal cell carcinoma.

Kugler A, Seseke F, Thelen P, Kallerhoff M, Muller GA, Stuhler G, Muller C, Ringert RH.

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OBJECTIVE: To evaluate the safety, acute and long-term toxicity and therapeutic activity of an allogenic and an autologous hybrid cell vaccine in patients with progressive metastatic renal cell carcinoma (RCC). PATIENTS AND METHODS: Eleven patients were vaccinated with a lethally irradiated hybrid cell vaccine of allogenic RCC tumour cells fused with major histocompatibility complex class I-matched and class II-unmatched activated allogenic lymphocytes. These patients were then followed for a mean of 11 months. Another 13 patients were vaccinated with a hybrid cell vaccine of autologous tumour cells fused with allogenic activated lymphocytes and followed for a mean of 6 months. RESULTS: Six of the 11 patients receiving the allogenic vaccination showed an initial response, with two complete and two partial responses to date. Only three patients who received autologous vaccination responded to treatment. CONCLUSIONS: Hybrid cell vaccination is a promising new approach in the treatment of patients with advanced RCC.

Publication Types:
- Clinical Trial

PMID: 9806175 [PubMed - indexed for MEDLINE]

1: Cancer Immunol Immunother 1993 May;36 (5):315-22

Adoptive immunotherapy of advanced melanoma patients with interleukin-2 (IL-2) and tumor-infiltrating lymphocytes selected in vitro with low doses of IL-2.

Arienti F, Belli F, Rivoltini L, Gambacorti-Passerini C, Furlan L, Mascheroni L, Prada A, Rizzi M, Marchesi E, Vaglini M, et al.

Division of Experimental Oncology D. Istituto Nazionale Tumori, Milan, Italy.

Freshly isolated tumor-infiltrating lymphocytes (TIL) from stage IV melanoma patients were cultured for 2 weeks with low doses of interleukin-2 (IL-2; 120 IU/ml), to select potentially for tumor-specific lymphocytes present in the neoplastic lesion, followed by high doses (6000 IU/ml) to achieve lymphocyte expansion. TIL were serially analyzed for their expansion, phenotype and cytotoxic activity against autologous and allogenic tumor cells. A preferential lysis of autologous melanoma cells was obtained in long-term cultures of 7/13 cases (54%), while the remaining ones showed a major-histocompatibility-complex-unrestricted, lymphokine-activated-killer(LAK)-like activity at the time of in vivo injection. Sixteen patients with metastatic melanoma were infused with TIL (mean number: 6.8 x 10(9), range: 0.35 x 10(9)-20 x 10(9)) and IL-2 (mean dose: 130 x 10 (6) IU, range: 28.8 x 10(6)-231 x 10(6) IU); 1 complete and 3 partial responses were observed in 12 evaluable patients (response rate 33%). In all responding patients, injected TIL showed an in vitro preferential lysis of autologous tumor cells, while in no cases were TIL with LAK-like activity associated with a clinical response. The mean autologous tumor cytotoxic activity of TIL at the time of in vivo injection was significantly higher in responding patients in comparison to nonresponding ones, suggesting that a marked and preferential cytolysis of autologous tumor cells is associated with the therapeutic efficacy of TIL.

PMID: 8477417 [PubMed - indexed for MEDLINE]

1: Cancer Immunol Immunother 1988;26 (1):74-82

Clinical adoptive chemoimmunotherapy with allogeneic alloactivated HLA-haploidentical lymphocytes: controlled induction of graft-versus-host-reactions.

Kohler PC, Hank JA, Minkoff DZ, Sondel PM.

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A total of 13 cancer patients were treated with Adoptive Chemoimmunotherapy (ACIT) using alloactivated HLA haploidentical lymphocytes. Donor lymphocytes were activated in vitro using a pool of irradiated allogeneic lymphocytes (MLC-cells) and some further expanded by culturing in T-cell growth factor (TCGF-cells). The first 6 patients received i.v. cyclophosphamide (CPM) followed 24 h later by escalating doses of MLC-cells, then 7 days later they received an infusion of TCGF-cells. Minimal toxicity was seen. The next 7 patients received CPM (800 mg/m2) and a combined MLC and TCGF-cell infusion (total cell dose ranged from 0.79 x 10(10) to 2.26 x 10(10)). Of these 7 patients, 3 developed mild graft-versus-host reaction (GVHR) which resolved without treatment, and 2 patients had progressive GVHR which was arrested by methylprednisolone (2 mg/kg). Peripheral blood lymphocytes from these 2 patients, during the GVHR, had increased activated T-cells (OKT-10+ and OK-Ia+). In vitro expansion, in TCGF, of these activated T-cells enabled HLA typing to prove they were of donor origin. Only 1 clinical antitumor response was observed in the first 6 patients. The results of this study indicate that this form of ACIT can be given to patients with acceptable toxicity. Self-limited or easily controlled GVHR may be induced and donor cells persisting in the circulation are probably responsible. Further testing is required to determine whether the immune response induced by this form of ACIT may be therapeutically effective.

PMID: 3257904 [PubMed - indexed for MEDLINE]

☐ 1: J Reprod Immunol 2000 Feb;46(1):51-7

Neonatal thrombocytopenia induced by maternal anti-HLA antibodies: a potential side effect of allogenic leukocyte immunization for unexplained recurrent aborters.

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Allogenic leukocyte immunization is one of several treatments tried for unexplained recurrent aborters, and is reported to have few maternal and neonatal side effects after the immunotherapy having been reported to date. In the present study, we report a rare case of neonatal thrombocytopenia (41000 cells/microl) observed in a female infant delivered by an unexplained habitual aborter. The mother was immunized with her husband's leukocytes once before pregnancy and twice at the 5th and 6th week of her successful pregnancy. Serological studies using mixed passive hemagglutination assays (MPHA) showed that maternal serum did not contain any antibodies which were reactive to 11 platelet-specific antigens, or to granulocyte antigens extracted from 9 persons. Lymphocyte cytotoxicity tests, however, showed that maternal serum but not infant serum had anti-HLA antibodies against both paternal and infant lymphocytes. Moreover, the maternal serum was found to have anti-HLA IgGs against platelet antigens extracted from the father and the infant. It is highly likely that this case of neonatal thrombocytopenia was caused by transplacental perfusion of maternal anti-HLA antibodies whose production was induced or enhanced by the allogenic leukocytes immunizations.

PMID: 10708244 [PubMed - indexed for MEDLINE]

1: Eur J Immunol 1993 Aug;23(8):2022-5

Alloactivated cytotoxic T cells recognize the carboxy-terminal domain of human immunodeficiency virus-1 gp120 envelope glycoprotein.

Clerici M, Shearer G, Hounsell EF, Jameson B, Habeshaw J, Dalgleish AG.

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Infection with the human immunodeficiency virus (HIV) virus leads to clinical disease in humans but not in chimpanzees. Progression to disease is associated with activation of the immune system followed by loss of T helper cell function and a slow decline in CD4-positive lymphocytes. The presence of autoreactive and cytotoxic cells in humans but not chimpanzees suggests that mechanisms other than. or in addition to. direct virus-induced cell killing, are required for disease to develop. The observed changes are similar to those seen in chronic allogeneic disease. Here we show that a peptide from the carboxy terminus of gp120, predicted to have a structure similar to the major alpha-helices of major histocompatibility complex (MHC) class I and class II, acts as a cytolytic target when presented on syngeneic cells for alloactivated cytotoxic T effector cells. These data add further evidence to the hypothesis that HIV can act as an allostimulant due to its dual properties of CD4 binding and MHC mimicry. The ability to signal nonspecifically through the T cell receptor could explain the initially paradoxical responses of proliferation, anergy and apoptosis.

PMID: 8344368 [PubMed - indexed for MEDLINE]